PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/013445	26.11.2004	28.11.2003

International Patent Classification (IPC) or both national classification and IPC
A61K39/395, C07K16/28, C07K16/46

Applicant
MICROMET AG

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2004/013445

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed.

   ☒ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 20,22-25 (all partially)

because:

☒ the said international application, or the said claims Nos. 20,22-25 (all with respect to industrial applicability) relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form ☐ has not been furnished

☐ does not comply with the standard

the computer readable form ☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☐ paid additional fees.

   ☒ paid additional fees under protest.

   ☐ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☒ complied with

   ☐ not complied with for the following reasons:

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos.

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	5-18
	No:	Claims	1-4,19-25
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-25
Industrial applicability (IA)	Yes:	Claims	1-19,21
	No:	Claims	

2. Citations and explanations

   see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

The present application describes the use of a composition, e.g. bispecific antibodies (mainly directed against CD3 and CD19 or EpCAM), in therapy.

The following document (D) is referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D2: EP-A-1 348 715 (MICROMET AG) 1 October 2003

Re Item III
Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 20,22-25 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item IV
Lack of unity of invention

The applicant's protest regarding the allegation of non-unity filed with the letter dated August 18, 2005, is admissible (Rule 40.2(c) PCT) and the objection of lack of unity of invention has been withdrawn.

Re Item V
Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-4,19-25 is not new in the sense of Article 33(2) PCT.

The document D2 discloses (the references in parentheses applying to this

document): a monomeric (page 19, lines 12-15; Fig. 10; Fig. 11) bispecific anti-CD19/anti-CD3 single chain antibody construct with no detectable impurities (page 19, lines 12-15; Fig. 10; Fig. 11, lane 5) that eliminates chronic lymphocytic leukemia B cells (example 7), non-Hodgkin lymphoma (claim 25) and B-cell mediated autoimmune diseases (claim 30) and that destroys malignant B cells by T cells through the cytotoxic activity of bscCD19xCD3 (page 18, paragraph 79; page 21, paragraph 95). The bispecific anti-CD19/anti-CD3 single chain antibody construct has SEQ ID NO:10, in which amino acid residues 28-531 are 100% identical to the entire SEQ ID NO:1 of the present application.

Concerning the subject-matter of claim 19 it should be mentioned that a product is not rendered novel by the fact that it is produced by a potentially new process (PCT Guidelines Appendix A5.26[1], 2004).

2 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 5-18 does not involve an inventive step in the sense of Article 33(3) PCT.

The document D2 is regarded as being the closest prior art to the subject-matter of claims 5-18, and discloses besides the disclosures as stated above: a method to purify monomeric bscCD19xCD3 using:

a) cation exchange chromatography followed by elution with 0.45 M NaCl,
b) Cobalt chelate affinity chromatography followed by elution with 0.5 M imidazole and
c) gel filtration to obtain a 50 to 70 kDa size fraction (Fig. 10)

which contains the monomeric bscCD19xCD3 without any detectable impurities (Fig. 45, lane 5).

The subject-matter of claims 5-18 therefore differs from document D2 in the order of the columns used to obtain a composition comprising a monomeric polypeptide comprising at least two antigen binding sites one of which is specific for CD3 and in which the monomeric form has been enriched relative to the amount of said polypeptide in multimeric form.

The problem to be solved by the present invention may therefore be regarded as providing an alternative method to obtain a composition comprising a monomeric polypeptide comprising at least two antigen binding sites one of which is specific for CD3 and in which the monomeric form has been enriched relative to the amount of said polypeptide in multimeric form.

The solution to this problem proposed by the present application consists of the provision of a method to obtain a composition comprising a monomeric polypeptide comprising at least two antigen binding sites one of which is specific for CD3 and in which the monomeric form has been enriched relative to the amount of said polypeptide in multimeric form, comprising:

a) a first chromatographic material comprising a metal ion followed by elution with at least 60 mM imidazole,
b) a second chromatographic material which is an ion exchange material and followed by elution with sodium chloride of at least 200 mM and
c) a third chromatographic material allowing separation on the basis of molecular weight

and analysing the obtained fraction.

Document D2 already discloses the single chromatographic steps and changing the order of these steps appears not to result in any surprising technical effect that could make a contribution over the prior art. Instead, by carrying out the steps as described in D2 the person skilled in the art would inevitably arrive at a composition as described in claim 1 of the present application, i.e. monomeric bscCD19xCD3 without any detectable impurities (page 19, lines 12-15; Fig. 10; Fig. 11, lane 5).

Thus, the subject-matter of claims 5-18 does not involve an inventive step (Article 33(3) PCT).

3 The subject-matter of claims 1-19,21 is susceptible of industrial application (Article 33(4) PCT).

4 For the assessment of the present claims 20,22-25 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The

patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VIII
Certain observations on the international application

5 Present claims 1-25 relate to compounds defined by reference to a desirable characteristic or property, namely by being a composition comprising a polypeptide comprising at least two antigen binding sites one of which is specific for CD3 (claim 1).
The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds, i.e.: only for antigen binding sites comprising the heavy and light chain of an antibody (e.g. example 2b).

Therefore, the subject-matter of claims 1-25 does not meet the requirements of Articles 5 and 6 PCT because the subject-matter is not sufficiently disclosed and supported.

6 The subject-matter of claim 19 is defined in the term of process for its preparation ('product-by-process' claims).
Claims for products, defined in terms of a process of manufacture, are considered as meeting the requirements of Article 6 PCT provided there is no other information available in the application, which could enable the applicant to define the product satisfactorily by reference to its composition, structure or some other testable parameter.
In consequence, the conditions to define a product by its process of production are that there are no other parameters available for a further definition of the product,

which is not the case here.

7 Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the document D2 is not mentioned in the description, nor is this document identified therein.